Prostate Cancer™ UPDATE

Conversations with Urologic Oncology Investigators

Bridging the Gap between Research and Patient Care

SPECIAL ISSUE

Proceedings from a Clinical Investigator "Think Tank"

EDITOR

Neil Love, MD

PANEL MEMBERS

Gerald W Chodak, MD
E David Crawford, MD
Mario A Eisenberger, MD
Stephen J Freedland, MD
Leonard G Gomella, MD
Thomas E Keane, MBBCh
Laurence Klotz, MD
Daniel P Petrylak, MD
Paul F Schellhammer, MD
Howard I Scher, MD
Michael J Zelefsky, MD
Craig D Zippe, MD

CME Certified

Subscribe to Podcasts or download MP3s of this program at ProstateCancerUpdate.com/ThinkTank

Prostate Cancer Update
A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Prostate cancer is one of the most rapidly evolving fields in urologic oncology. Published results from clinical trials lead to the emergence of new surgical and radiation therapy techniques and therapeutic agents, along with changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing urologist and radiation oncologist must be well informed of these advances. To bridge the gap between research and practice, Prostate Cancer Update utilizes a moderated forum with leading urologic oncology and radiation oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists urologists and radiation oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in prostate cancer screening, prevention and treatment and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Inform prostate cancer patients about the specific risks and benefits of local and systemic therapies.
- Provide individualized counseling to patients regarding the choice and timing of endocrine therapy.
- Counsel appropriately selected patients in the high-risk or advanced disease settings about the risks and benefits of chemotherapy, including emerging data on taxane-based regimens.

PURPOSE OF THIS ISSUE OF PROSTATE CANCER UPDATE

The purpose of this special edition of Prostate Cancer Update is to support these global objectives by offering the perspectives of Drs Chodak, Crawford, Eisenberger, Freedland, Gomella, Keane, Klotz, Petrylak, Schellhammer, Scher, Zelefsky and Zippe on the integration of emerging clinical research data into the management of prostate cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3.5 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the Post-test and Evaluation Form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ProstateCancerUpdate.com/ThinkTank** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**.

TABLE OF CONTENTS

TOPICS

If you would like to discontinue your complimentary subscription to *Prostate Cancer Update*, please email us at **Info@ResearchToPractice.net**, or fax us at (305) 377-9998. Please include your full name and address, and we will remove you from the mailing list.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

FACULTY AFFILIATIONS

Gerald W Chodak, MD
Director, Midwest Prostate and Urology Health Center
The University of Chicago
Chicago, Illinois

E David Crawford, MD
Professor of Surgery and Radiation Oncology
Head, Urologic Oncology
University of Colorado Health Sciences Center
Aurora, Colorado

Mario A Eisenberger, MD
R Dale Hughes Professor of Oncology and Urology
The Johns Hopkins University
Baltimore, Maryland

Stephen J Freedland, MD
Attending Physician
Durham VA Medical Center
Assistant Professor of Urology and Pathology
Duke University School of Medicine
Durham, North Carolina

Leonard G Gomella, MD
The Bernard W Godwin Professor of Prostate Cancer
Chairman, Department of Urology
Jefferson Medical College
Director of Urologic Oncology
Kimmel Cancer Center
Philadelphia, Pennsylvania

Thomas E Keane, MBBCh
Chairman and Professor
Medical University of South Carolina
Department of Urology
Charleston, South Carolina

Laurence Klotz, MD
Professor of Surgery
University of Toronto
Chief, Division of Urology
Sunnybrook and Women's College Health Sciences Center
Toronto, Ontario

Daniel P Petrylak, MD
Associate Professor of Medicine
Director, Genitourinary Oncology Program, Columbia Presbyterian Medical Center
New York, New York

Paul F Schellhammer, MD
Professor, Eastern Virginia Medical School
Norfolk, Virginia

Howard I Scher, MD
D Wayne Calloway Chair in Urologic Oncology
Chief, Genitourinary Oncology Service
Memorial Sloan-Kettering Cancer Center
New York, New York

Michael J Zelefsky, MD
Chief, Brachytherapy Service
Memorial Sloan-Kettering Cancer Center
New York, New York

Craig D Zippe, MD
Co-Director, Prostate Center
Glickman Urological Institute
The Cleveland Clinic Foundation
Cleveland, Ohio

CONTENT VALIDATION AND DISCLOSURES

Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

The scientific staff and consultants for Research To Practice are involved in the development and review of content for educational activities and report the following real or apparent conflicts of interest for themselves (or their spouses/partners) that have been resolved through a peer review process: Richard Kaderman, PhD, Neil Love, MD, Douglas Paley, Margaret Peng, Lilliam Sklaver Poltorack, PharmD, Ginelle Suarez, Chris Thomson, MD, MS, Erin Wall and Kathryn Ault Ziel, PhD — no real or apparent conflicts of interest to report; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc and Genentech Inc. Research To Practice receives education grants from Abraxis Oncology, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Genentech Inc/OSI Pharmaceuticals Inc, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis, who have no influence on the content development of our educational activities.

In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Chodak — Speakers Bureau: Abbott Laboratories, AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals Corporation, Threshold Pharmaceuticals. **Dr Crawford** — Consulting Fees and Speakers Bureau: Auxilium Pharmaceuticals Inc, GlaxoSmithKline, Sanofi-Aventis. **Dr Eisenberger** — Consulting Fees: Amgen Inc, ImClone Systems, Merck and Company Inc, Sanofi-Aventis; Contracted Research: Celgene Corporation, Centocor Inc, Cytogen Corporation, Prostate Cancer Foundation, Sanofi-Aventis. **Dr Freedland** — Consulting Fees: AstraZeneca Pharmaceuticals LP; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP. **Dr Gomella** — Consulting Fees: GlaxoSmithKline; Speakers Bureau: AstraZeneca Pharmaceuticals LP, TAP Pharmaceuticals Inc. **Dr Keane** — Consulting Fees: AstraZeneca Pharmaceuticals LP, Auxilium Pharmaceuticals Inc, Sanofi-Aventis, Valera Pharmaceuticals; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP, Auxilium Pharmaceuticals Inc, Cytogen Corporation, Pfizer Inc. **Dr Klotz** — Consulting Fees: Abbott Laboratories, AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Merck and Company Inc, Sanofi-Aventis; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: Abbott Laboratories, AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Merck and Company Inc, Sanofi-Aventis. **Dr Petrylak** — Consulting Fees: Abbott Laboratories, Bristol-Myers Squibb Company, Celgene Corporation, Cell Genesys Inc, Centocor Inc, Dendreon Corporation, Eli Lilly and Company, GPC Biotech Inc, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, Sanofi-Aventis; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: Sanofi-Aventis; Contracted Research: Abbott Laboratories, Cell Genesys Inc, Eli Lilly and Company, GPC Biotech Inc, Sanofi-Aventis. **Dr Schellhammer** — Consulting Fees: Dendreon Corporation, Sanofi-Aventis; Contracted Research: AstraZeneca Pharmaceuticals LP, Sanofi-Aventis; Ownership Interest: Dendreon Corporation. **Dr Scher** — Contracted Research: AstraZeneca Pharmaceuticals LP, Sanofi-Aventis. **Dr Zelefsky** — Consulting Fees: Oncura, Varian Inc. **Dr Zippe** — Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: Pfizer Inc.

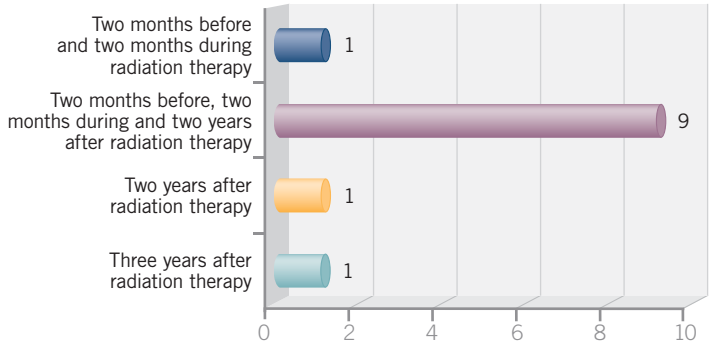
SECTION 1

MULTIMODALITY THERAPY FOR HIGH-RISK DISEASE

RADIATION THERAPY WITH ANDROGEN DEPRIVATION

FACULTY POLL QUESTION 1

A 74-year-old man with Stage cT3b, Gleason 8 prostate cancer and a PSA level of 6.2 ng/mL receives TRUS: 65 cc; IPSS: 22 and elects to be treated with intensity-modulated radiation therapy (IMRT) and androgen deprivation therapy (ADT). Which of the following do you consider the optimal sequence and duration of androgen deprivation therapy?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

Select Excerpts from the Discussion

CD 2, Track 15

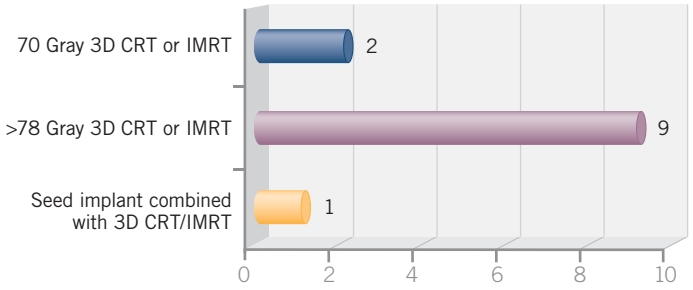
DR LOVE: Could you comment on the combination of high-dose radiation therapy and androgen deprivation for patients at high risk?

DR ZELEFSKY: Dose response data for patients at high risk suggest that a significant percentage of these patients may have localized disease warranting aggressive local therapy. However, it is unclear if a patient with low-volume, high-grade disease needs prolonged hormonal therapy or whether an aggressive course of local therapy is sufficient.

Currently, with IMRT conformal treatments, there's a slight increase in urinary side effects and chronic obstructive symptoms with the higher dose,

FACULTY POLL QUESTION 2

Which of the following do you consider the preferred form of radiation therapy for this patient?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

but this is not that significant clinically. The rectal bleeding rates have been only three percent despite applications as high as 86 Gray. We're examining the impact of the higher doses on quality of life, but I don't believe they make a tremendous difference in regard to toxicity.

DR KEANE: We know that 70 Gray combined with hormonal therapy works far better than 70 Gray alone.

The concern is that in the trials that are moving the radiation dose to 78 Gray, we have no idea how that dose combined with hormonal therapy will affect the patient in terms of toxicity. We know that increasing the radiation dose results in more toxicity.

DR CRAWFORD: Mike and others have clearly shown that escalating the dose of radiation increases the response rate with minimal side effects. However, I'm concerned about what we will see in these patients a decade later. We know that radiation therapy can have long-term sequelae.

DR LOVE: Mike, what long-term toxicity data do we have with high-dose radiation therapy?

DR ZELEFSKY: We now have data past 10 years, at least for 75 Gray of conformal radiation therapy, and we have not seen hemorrhagic cystitis, rectal strictures or the like.

The risk of developing secondary cancers is greater in these patients than in the general population, and they need to be followed. I agree that as we move into these uncharted trials of higher radiation doses, we need to look at the long-term toxicities in 10 and 15 years.

CD 2, Track 17

DR LOVE: Laurie, how do you decide on the duration of hormonal therapy with radiation treatment, and does it change based on the patient's age?

DR KLOTZ: The data are not that clear as to the optimal duration. In my practice, I use six months to three years of therapy, and I titrate it according to the patient's risk and the degree to which the patient tolerates hormonal therapy.

I believe six months of hormonal therapy is a bare minimum with these patients. In the face of the D'Amico study, the disease-free survival rate improvement was the same with six months of therapy as in other studies of two years in an intermediate-risk cohort (D'Amico 2004).

I'm not aware of any comparison of six months to longer durations in patients at higher risk, but the argument to go beyond six months is not so compelling that I would do so in a patient who is experiencing difficulty with the therapy.

DR ZELEFSKY: Although the D'Amico study never compared the two durations, the paper suggests that longer courses may be better. However, lower doses of radiation were used, so the role of higher doses remains unclear. Also, the way "high risk" has been described in trials is variable. Obviously, the volume of disease is a critical aspect, and maybe it should be based on volume rather than on these arbitrary nomenclatures of high risk.

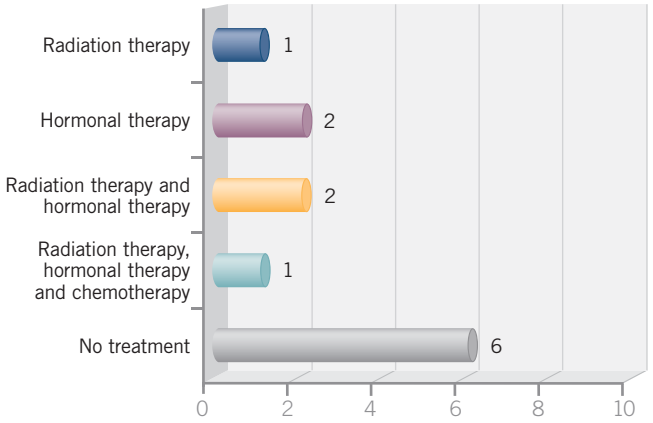
DR KEANE: The Hanks data compared goserelin and flutamide two months before and two months during radiation therapy with or without an additional 24 months of goserelin. In a subset analysis, the 28 months of therapy resulted in significantly better overall survival in the so-called patients at high risk (Hanks 2003). I believe that's the only hard evidence we have one way or the other.

DR CHODAK: There are a lot of good randomized trials, but I'm concerned that none of the studies is pure. Maybe you could argue that D'Amico's study is the best in the sense that there was a more limited group of intermediate-risk patients, but even there, patients could enroll with a high PSA or with a high Gleason score.

The lack of the homogeneity may, in part, explain why it takes 10 years to see a benefit in one RTOG trial, whereas we saw a benefit earlier in the Bolla trial (Bolla 2002). We may need to be more careful designing these trials. We want to get them done and include a lot of patients at high risk, but we may be camouflaging patients who actually have metastatic disease and would benefit from hormone therapy versus patients with extensive local disease, who would benefit from a higher dose of radiation. ■

FACULTY POLL QUESTION 3

A 57-year-old man with a PSA level of 6.3 ng/mL who was diagnosed with prostate cancer underwent an RRP one month ago. His pathology report shows a Gleason score of 9 (5 + 4), right seminal vesicle involvement and a positive surgical margin. Five of five nodes on the right and five of five on the left are negative for metastasis. The standard of care for this patient is:



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

CD 2, Track 18

DR LOVE: Len, do you feel the multimodality approach is appropriate when treating patients with high-risk disease after a prostatectomy?

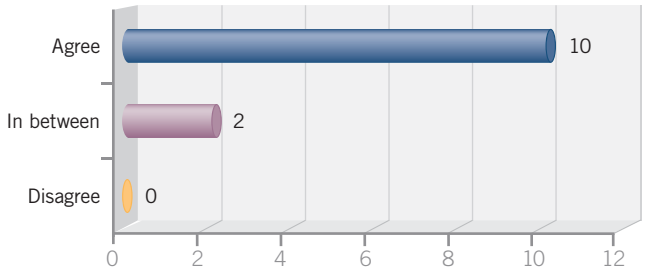
DR GOMELLA: We know that treatment outcomes relate to risk stratification and that patients at low risk have similar outcomes with any monotherapy and patients at high risk generally do not do well with standard monotherapy. The majority of patients who progress after therapy do have high-risk disease, and we know that high-risk disease accounts for most of the prostate cancer deaths.

What the best treatment is for patients at high risk is unclear, and we have limited data from clinical trials for this group of patients, so it's reasonable for us to be evaluating multimodality approaches for these patients.

In clinical practice, it's important for us to risk stratify each case, evaluate the postoperative data and discuss the options with our patients. One should consider adjuvant hormone therapy for patients with positive lymph nodes,

FACULTY POLL QUESTION 4

Men with very high-risk disease after radical prostatectomy should be informed about the possibility of receiving adjuvant androgen deprivation therapy outside a protocol setting.



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

based on the Messing study. One might question whether this could be the new standard of care for patients at high risk (Messing 2006).

In addition, we should attempt to place patients on randomized clinical trials because we really have a paucity of published data in this area.

DR LOVE: Steve, how do you approach the patient who has high-risk disease after radical prostatectomy?

DR FREEDLAND: I question whether it makes a difference if we treat the patient immediately versus monitoring the patient and, if he recurs, gaining more information — such as the PSA kinetics, the doubling time, the time to recurrence — to better risk stratify that patient. I believe, based on my view of the literature, that in most of these patients I have not lost anything by waiting.

I counsel my patients on the options, but I prefer the salvage route versus adjuvant therapy. Delaying treatment allows patients to recover their potency, their continence and the like.

In addition, a significant portion of men at high risk will not recur. Even in margin-positive disease, only 50 percent of those patients recur, so we can avoid therapy for some of those patients.

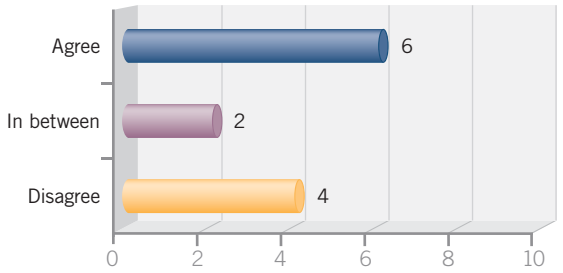
DR LOVE: How do you approach the patient with node-positive disease?

DR FREEDLAND: The Messing data show that if you treat now versus delaying until the time of metastatic disease, you're going to improve survival (Messing 2006).

However, although I believe the Messing data from the therapeutic arm, the control arm is not representative of my practice, so it's hard to say that they are meaningful data to me.

FACULTY POLL QUESTION 5

Men with very high-risk disease after radical prostatectomy should be informed about the possibility of receiving adjuvant bicalutamide monotherapy outside a protocol setting.



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

I would treat those patients once they recur, and the majority will recur with positive nodes, but not 100 percent. Even in the control arm, there were some men who were disease free for a long time. I believe you can avoid therapy in some men and treat those who really need it early enough so that you haven't lost anything.

CD 2, Tracks 19-20

DR LOVE: Paul, can you comment on the issue of treating the unusual patient with node-positive disease?

DR SCHELLHAMMER: I feel strongly that patients with node-positive disease have a high enough risk and the data are strong enough to initiate androgen deprivation therapy.

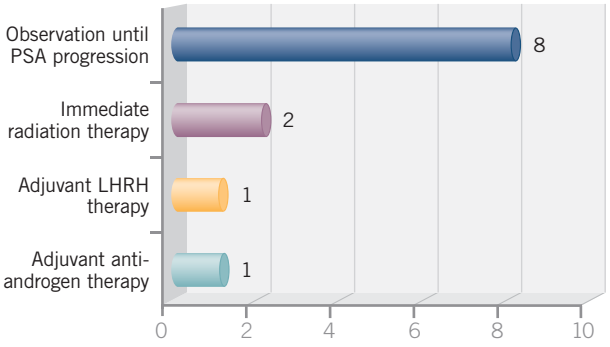
Patients at high risk, in general, are clinical trial candidates. However, if I have a patient who is not on a clinical trial and whom I'm going to follow with observation, my inclination is to get ultrasensitive PSAs from the get-go. Then I can determine the rising PSA before it gets to the 0.2 level that we have said is the beginning of failure. To me, that's the absolute indication to initiate another therapeutic option.

DR ZIPPE: I prefer to wait and watch for elevation of the PSA. I am a big fan of bicalutamide monotherapy. I look to treat with minimal side effects. I have patients now who are six and seven years out, and their disease is still undetectable.

DR KEANE: I believe we need to reconsider this high-risk situation and decide whether we are talking about palliation or cure. Examining the data from Bolla, Hanks, Messing and the RTOG-8531, I believe we can cure some of

FACULTY POLL QUESTION 6

A 61-year-old man undergoes a radical prostatectomy for Stage T2b, Gleason 7 (4 + 3) prostate cancer. His pathology report shows Stage T3b disease. One month later his PSA is undetectable. What should be done at this time?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

these patients (Bolla 2002; Hanks 2003; Messing 2006; Lawton 2005). When you look at the long-term data and the survival curves, after approximately seven to 10 years they begin to closely mirror the general population.

DR FREEDLAND: If you think it is curative, if you have a patient with positive nodes, you treat him with adjuvant androgen deprivation and his PSA remains undetectable, do you stop hormonal therapy at some point and see what happens?

DR KEANE: Absolutely. After five years we're measuring the testosterone levels and discontinuing the anti-androgens and the LHRH agonists because there must be a time point where you've burned out the hypothalamic pituitary axis.

The Bolla trial gave us the first inclination. I believe 25 or 30 percent of the patients never regained a normal testosterone level. That being the case, you may not improve the patients' side effects, because they'll still have the side effects of castration, but you save a considerable amount of money by discontinuing treatment.

DR FREEDLAND: If the patient's testosterone returns to normal, do you restart the therapy then?

DR KEANE: I would.

DR FREEDLAND: So you're not actually taking them off androgen deprivation, correct?

DR KEANE: Correct.

DR FREEDLAND: If the idea is that it's curative, there should be a point at which you've reached the cure and you could stop therapy, allow their testosterone to return to normal, and they should be fine.

DR KEANE: In theory, yes.

DR LOVE: Unless you define it as a functional cure, which is that they have the same life expectancy as an age-matched population. They may still have the tumor present, it might still need to be suppressed, but they're cured, clinically.

DR FREEDLAND: I would agree with that.

DR CRAWFORD: We published a paper a few years ago looking at the 10-year survival rates in metastatic cancer, and approximately eight to 10 percent of these people are alive at 10 plus years (Tangen 2003). In a lot of cancers, we call that a cure. So I agree that hormone therapy does cure some patients with prostate cancer. I don't think there is any question about it when evaluating the 13-year data we have right now. I mean, how long do we have to go before we call it a cure? ■

POSTPROSTATECTOMY RADIATION THERAPY

CD 3, Tracks 2-4

DR LOVE: Dave, can you discuss the role of adjuvant as opposed to salvage radiation therapy after radical prostatectomy?

DR CRAWFORD: With adjuvant radiation therapy, you have pros and cons. The pros are better biochemical control, better local control, potentially lower doses used and smaller tumors treated. The cons are no survival benefit has yet been demonstrated, treating many patients who don't need it, a lack of benefit if the patient has metastatic disease, increased cost and risk of unnecessary toxicity.

With salvage radiation therapy, the pros and cons are a little different. The pros are only treating those patients who are failing and increased cost effectiveness. The cons are delaying therapy, no benefits with metastases and treating larger tumors that are maybe less responsive.

DR LOVE: Steve, how do you approach the consideration of postprostatectomy radiation therapy?

DR FREEDLAND: According to the data published in *The Lancet* from EORTC-22911, about 50 percent of the patients with positive margins who were not treated with adjuvant radiation therapy had a PSA recurrence. Of

those patients with positive margins who were treated with adjuvant radiation therapy, about 70 percent did not have a PSA recurrence (Bolla 2005).

In Stephenson's data, there was about a 65 percent response to salvage radiation therapy among the select group of men who were eligible (Stephenson 2004). I think putting these two studies' results together makes a good argument for salvage radiation therapy. You are not treating the men who do not need it, and in the men who do need it, you are able to provide them an almost equally efficacious therapy at the time of recurrence.

DR ZELEFSKY: The data from SWOG-S8794 are important, but they do not yet demonstrate that if we followed patients carefully and on a detectable and bona fide rise in PSA, we could obtain the same disease-free survival benefit with radiation therapy. The interesting thing about the SWOG-S8794 data is that there was a crossover of patients, and it perhaps shows that earlier administration of radiation therapy compared to later will benefit patients.

Our practice, in general, even for a patient with a positive margin, is to discuss the options of adjuvant versus salvage radiation therapy. More often than not, we would recommend salvage radiation therapy on manifestation of a detectable and rising PSA.

DR CRAWFORD: I agree with Michael. In my practice I wait until the patient has a biochemical failure. If they have a failure, I treat them early.

DR GOMELLA: With postoperative radiation therapy, you have to remember a couple of things that may or may not be true. Number one, you do not radiate everybody; you radiate people with a high risk of recurrence. You figure out who is at risk for progression and then you offer them the radiation therapy.

DR LOVE: Lenny, can you describe a typical patient for whom you would use postoperative radiation therapy?

DR GOMELLA: We rely heavily on the Kattan nomogram (Stephenson 2005). If they have less than a 25 percent risk of recurrence after radical prostatectomy, based on their postoperative features, we mention it to them, but we do not usually recommend it.

For patients with a greater than 50 percent risk, we strongly recommend they consider adjuvant radiation therapy within three to six months of the radical prostatectomy. In those patients with a risk that is somewhere in between, we offer it as an option and let the patient decide. Ultimately the patients decide across the board, but we strongly encourage the patients with a greater than 50 percent recurrence risk to think about adjuvant radiation therapy.

DR LOVE: Mike, can you comment on the issue of morbidity?

DR ZELEFSKY: In the shorter term or even in the midrange post-treatment, we see exacerbation of stress incontinence. Increased numbers of bladder-neck strictures occur down the road, and there is an increased risk of proctitis.

Although the risks of serious injuries with the proper techniques remain low, it's incumbent upon anybody discussing postoperative or salvage radiation therapy to indicate that the morbidity will be increased above and beyond radical prostatectomy. We are increasing potential complications, albeit small.

DR KEANE: If you wait until the PSA starts to rise, are you going to do the patient a disservice? Is the disease going to have any poorer outcome? Has there ever been a head-to-head comparison of immediate versus delayed radiation therapy?

DR KLOTZ: A presentation at ASCO 2006 demonstrated that the response to salvage radiation therapy improved according to the PSA prior to radiation therapy, and the response was best when the PSA was below 0.2 ng/mL (MacDonald 2006).

It is clear that patients do better the earlier they are treated, if they need treatment. So pick the ones who are almost certainly going to progress and treat them because there is no point in waiting. Then for the rest, I think it's reasonable to take the small risk and wait. ■

POSTPROSTATECTOMY ADJUVANT SYSTEMIC THERAPY INCLUDING CHEMOTHERAPY

CD 3, Track 6

DR LOVE: Mario, can you review the ongoing adjuvant chemotherapy trials?

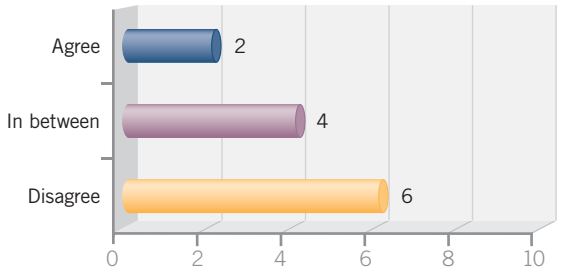
DR EISENBERGER: In SWOG-S9921, patients with high-risk disease are randomly assigned following radical prostatectomy to receive immediate hormonal therapy for two years with or without six months of mitoxantrone and prednisone. This study started in 1999, which was prior to the taxane era. The study is having difficulty in accrual, but I hope they will complete it. An issue with the trial is that it does not have a no-treatment control arm.

About three years ago, we conducted a pilot adjuvant feasibility trial evaluating docetaxel (Rosenbaum 2006). Patients had their pathology reviewed centrally at Johns Hopkins University, and we looked at the Rw model, which separates patients according to their probability of relapse. The trial was done before TAX-327 was reported (Tannock 2004), which is why we chose weekly docetaxel.

When we then plugged it into Mike Kattan's nomogram, we saw a shift suggesting a better outcome than predicted, but obviously this is very preliminary. The data, in addition to TAX-327, were what led us into the current study design.

FACULTY POLL QUESTION 7

Men with very high-risk disease after radical prostatectomy should be informed about the possibility of receiving adjuvant chemotherapy outside a protocol setting.



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

TAX-3501 includes patients who have no more than a 60 percent probability of remaining disease free at five years by the Kattan nomogram (Stephenson 2005). Patients are randomly assigned to either observation with treatment at the time of progression or immediate treatment. In both groups, patients are randomly assigned to 18 months of leuprolide with or without docetaxel. Essentially, this trial evaluates whether early treatment is more effective than deferred treatment.

CD 3, Track 7

DR PETRYLAK: I think we need to complete SWOG-S9921. If we change our chemotherapy every time some new results come out, we're never going to be able to complete a randomized trial.

DR CRAWFORD: I agree. We need to complete these trials. We're 20 years behind other tumors. Regarding SWOG-S9921, docetaxel was around when we designed the trial, but we thought we should use something that was better tolerated. There were other tumors that were using less aggressive chemotherapy. I think the downside of the trial is we don't have a no-treatment control arm. ■

SELECT PUBLICATIONS

Bolla M et al; European Organization for Research and Treatment of Cancer. **Postoperative radiotherapy after radical prostatectomy: A randomised controlled trial (EORTC trial 22911).** *Lancet* 2005;366(9485):572-8. **Abstract**

Bolla M et al. **Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial.** *Lancet* 2002;360(9327):103-6. **Abstract**

Carlini P et al. **Hormonal adjuvant treatment plus radiotherapy versus exclusive radio-**

therapy in locally advanced prostate cancer: Pooled analysis of 6 randomized trials. *Proc ASCO* 2006;**Abstract 4642**.

D'Amico AV et al. **Six-month androgen suppression plus radiation therapy compared with radiation therapy alone for men with prostate cancer and a rapidly increasing pretreatment prostate-specific antigen level.** *J Clin Oncol* 2006;24(25):4190-5. **Abstract**

D'Amico AV et al. **6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial.** *JAMA* 2004;292(7):821-7. **Abstract**

Eisenberger MA. **A multi-institutional pilot study of adjuvant docetaxel for patients with prostate cancer at high risk for relapse after radical prostatectomy.** *Rev Urol* 2003;5(Suppl 2):42-7. **Abstract**

Glode LM. **The case for adjuvant therapy for prostate cancer.** *J Urol* 2006;176(6 Suppl):30-3. **Abstract**

Gomella LG. **Addressing the needs of the high-risk prostate cancer patient.** *Rev Urol* 2005;7(Suppl 5):18-28. **Abstract**

Hanks GE et al; Radiation Therapy Oncology Group. **Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02.** *J Clin Oncol* 2003;21(21):3972-8. **Abstract**

Kumar S et al. **Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer.** *Cochrane Database Syst Rev* 2006;(4):CD006019. **Abstract**

Lawton CA et al. **Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: Updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31.** *J Clin Oncol* 2005;23(4):800-7. **Abstract**

MacDonald OK et al. **Predicting men at high risk for PSA failure after salvage radiotherapy for rising PSA following prostatectomy.** *Proc ASCO* 2006;**Abstract 4570**.

Messing EM et al. **Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy.** *Lancet Oncol* 2006;7(6):472-9. **Abstract**

Miller DC et al. **Incidence of initial local therapy among men with lower-risk prostate cancer in the United States.** *J Natl Cancer Inst* 2006;98(16):1134-41. **Abstract**

Peeters ST et al. **Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy.** *J Clin Oncol* 2006;24(13):1990-6. **Abstract**

Rosenbaum E et al. **Adjuvant weekly docetaxel for high-risk prostate cancer patients following radical prostatectomy.** *Proc ASCO Prostate Cancer Symposium* 2006;**Abstract 84**.

Stephenson AJ et al. **Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy.** *J Clin Oncol* 2005;23(28):7005-12. **Abstract**

Stephenson AJ et al. **Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy.** *JAMA* 2004;291(11):1325-32. **Abstract**

Tangen CM et al. **Ten-year survival in patients with metastatic prostate cancer.** *Clin Prostate Cancer* 2003;2(1):41-5. **Abstract**

Tannock IF et al; TAX 327 Investigators. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12. **Abstract**

Zeliadt SB et al. **Survival benefit associated with adjuvant androgen deprivation therapy combined with radiotherapy for high- and low-risk patients with nonmetastatic prostate cancer.** *Int J Radiat Oncol Biol Phys* 2006;66(2):395-402. **Abstract**

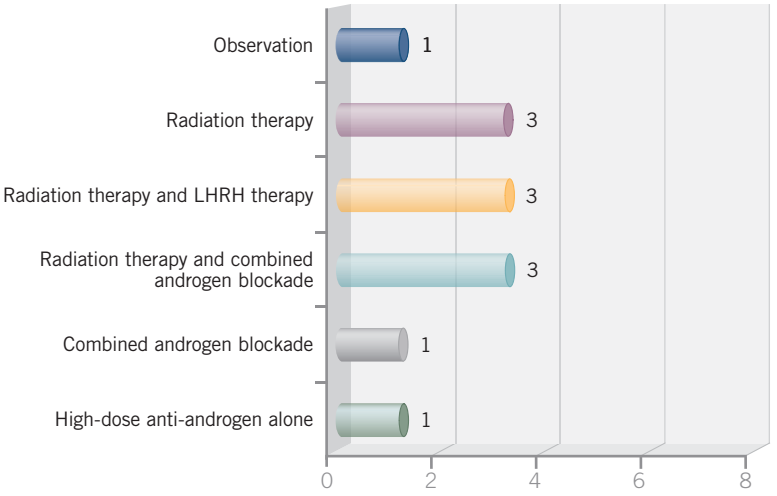
SECTION 2

TREATMENT FOR PATIENTS WITH PSA-ONLY RELAPSE

PSA DOUBLING TIME AND PROGNOSIS

FACULTY POLL QUESTION 8

A 60-year-old healthy man underwent a radical prostatectomy 12 months ago. He was diagnosed with Gleason 8, Stage T3a prostate cancer, with positive margins. He is continent and potent. After six months his PSA level was 0.2 ng/mL, at nine months it was 0.4 ng/mL, and at 12 months it was 0.8 ng/mL. What would you recommend?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

Select Excerpts from the Discussion

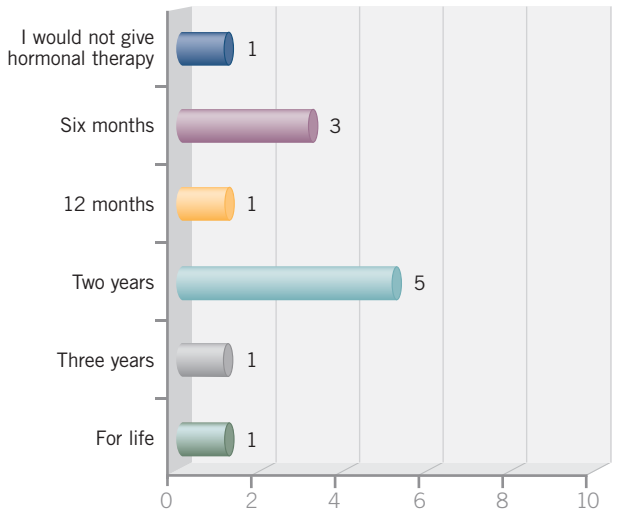
CD 1, Tracks 10-11

DR LOVE: Could you review your work at Johns Hopkins on the prognosis of men with PSA-only relapse?

DR FREEDLAND: The purpose of our study (Freedland 2005) was to examine risk factors for prostate cancer death with a patient population that was largely similar to that in Pound's study (Pound 1999). We studied more than 5,000

FACULTY POLL QUESTION 9

If you were going to administer radiation therapy and hormonal therapy to this patient, what would be the duration of the hormonal therapy?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

cases with nearly 1,000 recurrences, and 379 men had PSA doubling time data. Of those 379, 66 died of prostate cancer and 15 died of nonprostate cancer causes. So about three quarters of the deaths in our study on an actuarial basis were due to prostate cancer. It's a young, healthy Johns Hopkins cohort in which we're not seeing a lot of competing mortalities, so we obtained a long natural history of prostate cancer. Now we are up to 10 years of follow-up.

Overall, we confirmed the long natural history of prostate cancer we saw in the Pound series (Pound 1999), which was, on average, 13 years from recurrence to death. In our series it was more like 16 years.

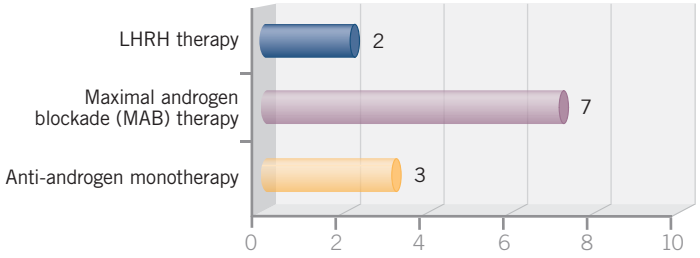
When we assessed risk factors for prostate cancer death, we found exactly the same risk factors that predict metastatic disease and death from prostate cancer: PSA doubling time, early versus late recurrences and Gleason score.

For doubling time, the hazard ratio of 0.86 indicates that a one-month change in doubling time reduces the risk of death by 14 percent.

Absolutely capturing the real doubling time involves a lot of logistical issues and difficulties such that, at the end of the day, we wanted to regard it as a categorical variable. So we considered various cut points and eventually identified four categories. A doubling time greater than 15 months presented the

FACULTY POLL QUESTION 10

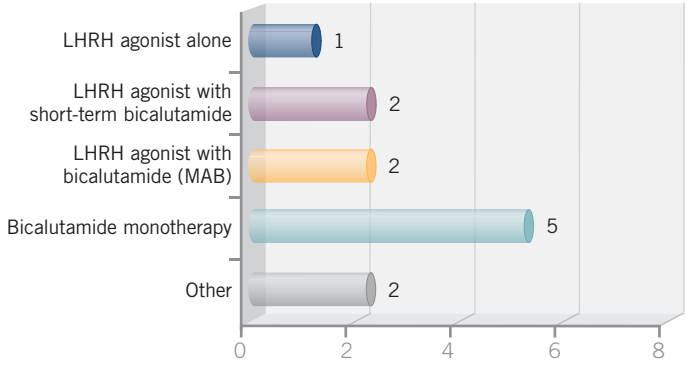
A 61-year-old man undergoes a radical prostatectomy for Stage T2b, Gleason 7 (4 + 3) prostate cancer. His pathology report shows Stage T3b disease. Two years later, the patient's PSA level is 0.6 ng/mL and doubles every three months, reaching 3.6 ng/mL. A bone scan is negative. The patient is sexually active. What systemic therapy, if any, would you advise?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

FACULTY POLL QUESTION 11

If you were diagnosed with PSA-only relapse two years after a radical prostatectomy that required hormone therapy and you had good sexual function at that point, which treatment would you likely prefer?

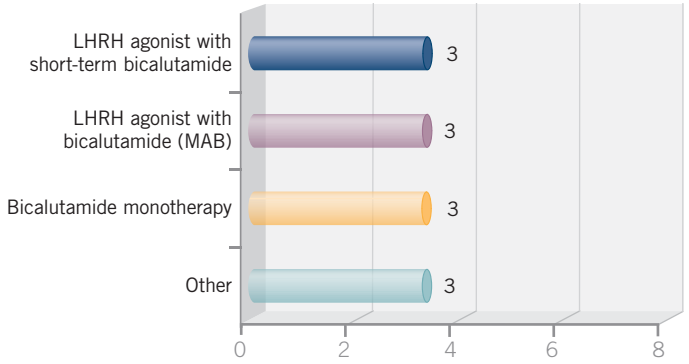


SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

lowest risk, and a doubling time less than three months presented a risk of dying from prostate cancer 27 times higher — these patients are at extremely high risk. With a PSA doubling time of three to nine months, patients are nine times more likely to die, and even with a PSA doubling time of nine to 15 months, patients are also at increased risk.

FACULTY POLL QUESTION 12

If you were diagnosed with PSA-only relapse two years after a radical prostatectomy that required hormone therapy and you had minimal erectile function, what treatment would you likely prefer?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

What we've shown is that men with rapid doubling times, high Gleason scores and early recurrence are at increased risk of prostate cancer death. We've generated tables that can predict that. Men who experience late recurrence generally have excellent survival, and time to recurrence, in the absence of knowing the doubling time, is an important prognostic feature. ■

CURRENT RESEARCH ON CHEMOTHERAPY FOR PSA RELAPSE

CD 1, Track 21

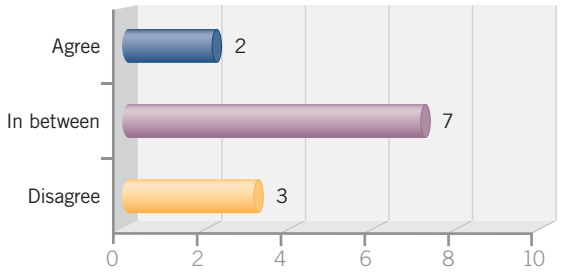
DR LOVE: Dave, do you refer patients with hormone-refractory PSA-only disease to a medical oncologist to consider nonprotocol chemotherapy?

DR CRAWFORD: I find the urologists are all pumped up about this, but the medical oncologists are hesitant to treat them with chemotherapy off protocol.

DR PETRYLAK: I believe that after carefully discussing with the patient the risks and benefits of chemotherapy, in some cases, it's totally appropriate to treat patients in that setting. We really don't know what the proper sequence is between secondary hormonal manipulations and chemotherapy, and now immune therapy is coming on board, but I do believe it's appropriate to consider it.

FACULTY POLL QUESTION 13

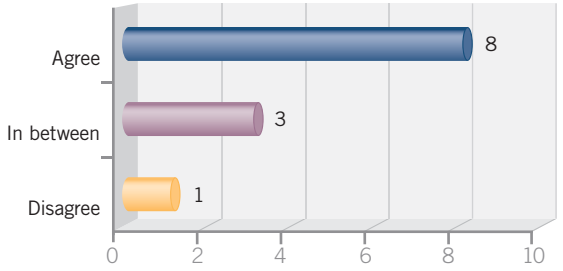
It is reasonable to offer chemotherapy to select (eg, very young, high-risk) patients with PSA-only relapse as part of initial therapy with androgen deprivation.



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

FACULTY POLL QUESTION 14

It is reasonable to offer chemotherapy in a clinical setting to some patients with PSA-only relapse whose disease has become refractory to hormone therapy.



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

DR FREEDLAND: There was a study published in the *Journal of Clinical Oncology* that showed chemotherapy is active for hormone-naïve disease (Goodin 2005; Hussain 2005).

However, chemotherapy relies on dividing, growing cells, and hormonal therapy puts most of the cells into a G0 arrest, so there may not be a benefit in combining the two at that early stage of the game. So off protocol, I'm hesitant to do it.

DR GOMELLA: The medical oncologists I work with at Jefferson basically try multiple alternative therapies before they actually commit somebody to chemotherapy.

When we send them a patient with hormone-refractory disease, their favorite thing to use is high-dose bicalutamide. Our medical oncologists are not directly jumping to a docetaxel-based therapy before they burn a lot of other bridges in between.

DR KLOTZ: Are we talking about hormone-naïve or hormone-refractory disease? I don't think anyone is advocating chemotherapy alone, without hormone therapy, for hormone-naïve disease.

DR LOVE: No, we are talking about adding it in.

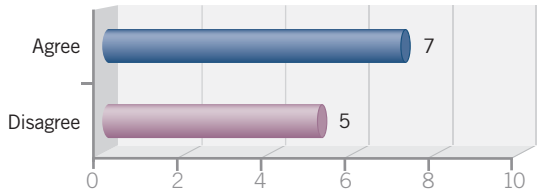
DR SCHER: This is part of the open question. We don't know how to optimally combine hormones and chemotherapy. As pointed out, if the cells are not dividing, we don't know that they're sensitive to specific types of agents.

DR KLOTZ: Off protocol, no one is advocating chemotherapy without hormone therapy for anything, except maybe in the neoadjuvant setting. ■

COMBINED ANDROGEN BLOCKADE

FACULTY POLL QUESTION 15

Combined androgen blockade offers a clinically meaningful survival benefit compared to androgen deprivation monotherapy.



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

CD 2, Tracks 2, 4-6

DR LOVE: Paul, can you review the data on combined androgen blockade (CAB)?

DR SCHELLHAMMER: In 2000, the Prostate Cancer Trialists' Collaborative Group did a meta-analysis and found a 2.9 percent five-year survival benefit in patients receiving CAB with flutamide and nilutamide (Prostate Cancer Trialists' Collaborative Group 2000). In a trial with more than 800 patients with metastatic disease that compared two different CAB constructs — bicalutamide versus flutamide — there was a trend to benefit in survival for patients on the bicalutamide arm.

Currently, there is a trial in Japan comparing an LHRH agonist with or without bicalutamide. The preliminary data show an advantage in PSA progression and progression to hormone-refractory disease for adding bicalutamide (Akaza 2004).

DR LOVE: What about the issue of cost?

DR SCHELLHAMMER: An analysis by Dave Penson of CAB therapy with bicalutamide shows an overall quality-adjusted and overall per-year-of-life gain that is reasonable with bicalutamide for MAB. It's within the construct of what we accept from renal dialysis in patients with renal failure (Ramsey 2005).

DR CRAWFORD: I believe CAB is the gold standard. It has plenty of data from large randomized Phase III trials to support it. None of the studies were negative, and I believe there is a reason to give it to patients with metastatic disease.

DR KEANE: The older studies dealt with patients with more advanced disease. If you examine the Dijkman and Janknegt studies, patients whose PSAs nadired down to less than 0.5 had a seven-month statistically significant survival advantage in heavy-volume metastatic disease (Dijkman 1995, 1997; Janknegt 1993).

We probably underestimated the effect of CAB and mistreated most of the patients. If you have a patient you plan to treat with an LHRH agonist, I would recommend CAB.

DR CHODAK: Not to be critical here, but the message that came out of Hopkins in response to CAB and the Peto analysis changed the attitude of many people. They feel the benefit is not worth the expense, and that is unfortunate because the benefit is greater than it is with docetaxel, and everyone is excited about docetaxel.

Now the truth is, we don't have a lot of patients who qualify based on metastatic disease. However, we do have a group of patients who are doubling in less than three months and dying within five to six years. They must have metastatic disease to be doing that.

Maximum blockade gives you the best chance for survival when you have metastatic disease, and treating earlier metastatic disease is better. We have a parameter that is identifying people who are acting like they have metastases, but we can't prove it, other than this PSA doubling time. Shouldn't we be aggressively using maximum blockade in that setting?

DR SCHER: I believe those patients need systemic therapy, and the standard for those patients is maximum blockade.

DR ZIPPE: I believe CAB got a bad name because we were throwing it at everyone, including patients whom the urologists knew had 10 years to live. I believe now that we can stratify patients and show the five-year mortality rates, CAB will be well accepted for a subset of patients.

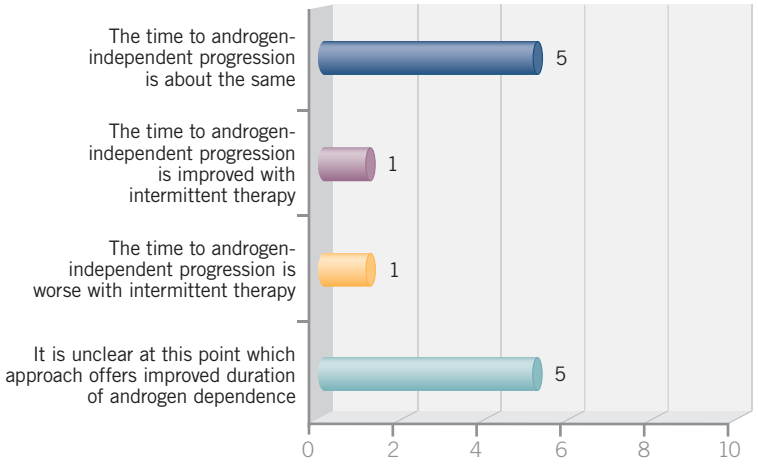
DR FREEDLAND: I believe part of the confusion comes when you evaluate the data on cyproterone acetate, which actually worsened survival. Some of the early meta-analyses that came out in *The Lancet* in the late 1990s actually showed no statistical benefit. That is the era when I was coming up in urology. I remember as a medical student saying, "Okay, combined androgen blockade does not add anything."

Then some of the reanalyses, taking the cyproterone acetate data, which is a steroidal anti-androgen — rather than the nonsteroidal bicalutamide — out of the equation, you start to see modest benefit, and I believe that clouds the picture. I am not sure the entire community of urologists is necessarily aware of the data if they just received the original *Lancet* paper from 1997 and read, "Overall, there is no benefit." ■

INTERMITTENT ANDROGEN DEPRIVATION

FACULTY POLL QUESTION 16

Intermittent therapy has been evaluated in a number of Phase 2 and Phase 3 studies. The evidence to date regarding intermittent compared to continuous androgen deprivation suggests that _____.



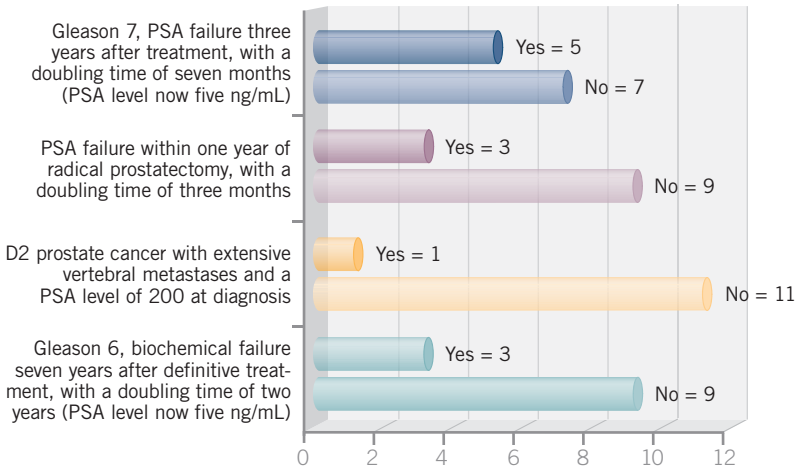
SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

CD 2, Tracks 8-9

DR LOVE: Laurie, would you describe the role of intermittent androgen deprivation?

FACULTY POLL QUESTION 17

Is intermittent therapy appropriate for the following cases?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

DR KLOTZ: The role of intermittent therapy has been clouded by the tremendous enthusiasm for early androgen deprivation therapy in patients with biochemical failure. I believe the question of early versus delayed therapy is still unanswered.

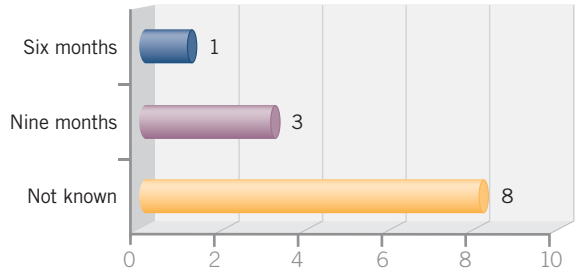
Studer reported at the AUA on a European trial of early versus delayed therapy in 900 patients (Studer 2005). They found no difference in time to progression, and the only patients who benefited from early therapy were those who had a PSA doubling time of less than a year.

There is a paradoxical dual effect of androgens on prostate epithelium. The direct effect is differentiation and, at some concentration, cell cycle arrest, whereas the indirect effect on the stroma, mediated by a number of growth factors, is proliferation. Thus you have two phenomena, differentiation and arrest induction and proliferation, so the idea that somehow testosterone is just a stimulator of prostate epithelial growth is not correct.

A trial initiated by Nick Berkoffsky 15 years ago shows us that re-exposure to testosterone may have an antiproliferative or differentiation-inducing effect. This trial of approximately 100 patients who received eight months of therapy demonstrated that the PSA lagged behind the testosterone; there's a window here that is predictive in terms of time to androgen-independent progression (Opfermann 2006).

FACULTY POLL QUESTION 18

The optimal duration of the induction period of intermittent therapy is _____.



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

The median time off therapy — and these were biochemical failures — was eight months, after an eight-month induction, and they found the off-treatment interval gets shorter with serial cycles.

They also observed that the baseline PSA was a major predictor of the off-treatment interval. Interestingly, there was consistently about a 95 percent reduction in the PSA regardless of the baseline.

The quality of life tended to return to baseline in the off-treatment interval in all domains. Six months after discontinuation of therapy, the vast majority of patients had at least 50 percent recovery of testosterone, although about half still were less than normal. Few patients experienced prolonged castrate levels.

The issue of the equivalence in terms of time to androgen independence has been a major point of controversy, and currently about five international trials are examining this.

Dave Crawford is leading a trial of intermittent therapy in metastatic disease, and we are leading one in Canada in biochemical failure after radiation therapy. None of these are mature, except for the Portuguese trial that has just been reported (Calais da Silva 2006).

In the Portuguese trial, 630 patients with locally advanced or metastatic disease were randomly assigned to intermittent versus continuous therapy with an LHRH analog plus cyproterone acetate, following three months of induction therapy. The Europeans tend to use three months of induction therapy, whereas in the United States and Canada it tends to be more like eight months to a year.

Although a lot of studies have reported preliminary results showing no difference in mortality, the event rate is low. However, in this trial the majority of patients have died, and prostate cancer was thought to be the cause in approximately two thirds of the deaths in both arms.

Despite stratification by PSA at randomization or metastatic status, there was no difference between therapies and absolutely no difference in survival.

I believe this is excellent support for the concept that the time to androgen-independent progression and prostate cancer survival is not significantly different between the two approaches.

CD 2, Track 12

DR ZIPPE: Laurie, I'm trying to determine where intermittent therapy might fit into the way we practice now. I used intermittent therapy with patients at lower risk. If you subset your data, did you find that the survival advantage was the same? Was intermittent therapy better for the patients with low-risk disease or worse for those with high-risk disease?

DR KLOTZ: No, the baseline parameters did not predict for a differential response with intermittent versus continuous therapy. Minor differences did arise, but they did not achieve any significance.

DR KEANE: The type of LHRH agonist utilized may also have an effect. A paper from last year showed that you can have up to seven months during which the LHRH — for instance, leuprolide — remains in the system, versus a depo preparation such as Viadur® or Vantas®. One of those is gone in six weeks. So part of the length of time that you are seeing an effect may be a function of the LHRH agonist that you are using and the delay in washout of those agents.

Secondly, it is interesting that we all multiply our PSAs by two when patients are on a 5-alpha reductase inhibitor. The division of the difference between the responses was almost exactly two. You had 15 months versus 30 months in terms of duration of treatment. That may have been a function of the PSA. We don't know, but it is certainly interesting to see that it's exactly half. ■

SELECT PUBLICATIONS

Akaza H et al. **Superior anti-tumor efficacy of bicalutamide 80 mg in combination with a luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist monotherapy as first-line treatment for advanced prostate cancer: Interim results of a randomized study in Japanese patients.** *Jpn J Clin Oncol* 2004;34(1):20-8. **Abstract**

Beer TM et al. **Phase I study of weekly mitoxantrone and docetaxel before prostatectomy in patients with high-risk localized prostate cancer.** *Clin Cancer Res* 2004;10(4):1306-11. **Abstract**

Calais Da Silva et al. **Phase III intermittent MAB vs continuous MAB.** *Proc ASCO* 2006;**Abstract 4513**.

Dijkman GA et al. **Long-term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. International Anandron Study Group.** *J Urol* 1997;158(1):160-3. **Abstract**

Dijkman GA et al. **Improved subjective responses to orchiectomy plus nilutamide (Anandron) in comparison to orchiectomy plus placebo in metastatic prostate cancer. International Anandron Study Group.** *Eur Urol* 1995;27(3):196-201. **Abstract**

Dreicer R et al. **Phase II trial of neoadjuvant docetaxel before radical prostatectomy for locally advanced prostate cancer.** *Urology* 2004;63(6):1138-42. **Abstract**

Eastham JA et al. **Cancer and Leukemia Group B (CALGB) 90203: A randomized phase 3 study of radical prostatectomy alone versus estramustine and docetaxel before radical prostatectomy for patients with high-risk localized disease.** *Urology* 2003;62(Suppl 1):55-62. **Abstract**

Febbo PG et al. **Neoadjuvant docetaxel before radical prostatectomy in patients with high-risk localized prostate cancer.** *Clin Cancer Res* 2005;11(14):5233-40. **Abstract**

Freedland SJ et al. **Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy.** *JAMA* 2005;294(4):433-9. **Abstract**

Garzotto M et al. **Neoadjuvant mitoxantrone and docetaxel for high-risk localized prostate cancer.** *Urol Oncol* 2006;24(3):254-9. **Abstract**

Goodin S et al. **Effect of docetaxel in patients with hormone-dependent prostate-specific antigen progression after local therapy for prostate cancer.** *J Clin Oncol* 2005;23(15):3352-7. **Abstract**

Hainsworth JD et al. **Weekly docetaxel/estramustine phosphate in patients with increasing serum prostate-specific antigen levels after primary treatment for prostate cancer: A phase II trial of the Minnie Pearl Cancer Research Network.** *Clin Genitourin Cancer* 2006;4(4):287-92. **Abstract**

Hussain A et al. **Docetaxel followed by hormone therapy in men experiencing increasing prostate-specific antigen after primary local treatments for prostate cancer.** *J Clin Oncol* 2005;23(12):2789-96. **Abstract**

Janknegt RA. **Total androgen blockade with the use of orchiectomy and nilutamide (Anandron) or placebo as treatment of metastatic prostate cancer. Anandron International Study Group.** *Cancer* 1993;72(12 Suppl):3874-7. **Abstract**

Klotz LH et al. **Intermittent endocrine therapy for advanced prostate cancer.** *Cancer* 1986;58(11):2546-50. **Abstract**

McKenzie MR et al. **Phase II study of neoadjuvant docetaxel and androgen suppression (AS) plus radiation therapy (RT) for high-risk localized prostate cancer (HRLCaP).** *Proc ASCO* 2006;**Abstract 4631**.

Mellado B et al. **Phase II trial of weekly docetaxel (D) and complete androgen blockade (CAB) prior to radical prostatectomy (RP) in high-risk localized prostate cancer (PC) patients (pts).** *Proc ASCO* 2006;**Abstract 14515**.

Opfermann KJ et al. **Intermittent hormone therapy in nonmetastatic prostate cancer.** *Clin Genitourin Cancer* 2006;5(2):138-43. **Abstract**

Pound CR et al. **Natural history of progression after PSA elevation following radical prostatectomy.** *JAMA* 1999;281(17):1591-7. **Abstract**

Prostate Cancer Trialists' Collaborative Group. **Maximum androgen blockade in advanced prostate cancer: An overview of the randomised trials.** *Lancet* 2000;355(9214):1491-8. **Abstract**

Ramsey S et al. **Is combined androgen blockade with bicalutamide cost-effective compared with combined androgen blockade with flutamide?** *Urology* 2005;66(4):835-9. **Abstract**

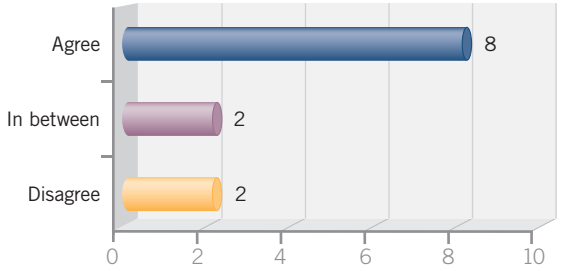
Southwest Oncology Group. **Quality of life and pain in advanced stage prostate cancer: Results of a Southwest Oncology Group randomized trial comparing docetaxel and estramustine to mitoxantrone and prednisone.** *J Clin Oncol* 2006;24(18):2828-35. **Abstract**

Studer UE et al. **Immediate versus deferred androgen deprivation in patients with asymptomatic prostate cancer T0-4 N0-2 M0 not suitable for local definitive treatment.** *Proc American Urologic Association* 2005;**Abstract 1659**.

Taplin ME et al. **Docetaxel, estramustine, and short-term androgen withdrawal for patients with biochemical failure after definitive local therapy for prostate cancer.** *Semin Oncol* 2001;28(4 Suppl 15):32-9. **Abstract**

FACULTY POLL QUESTION 19

Docetaxel-based chemotherapy is generally well tolerated.



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

Select Excerpts from the Discussion

CD 3, Tracks 11, 13

DR LOVE: Dan, can you review the clinical trials of docetaxel in patients with metastatic disease?

DR PETRYLAK: Two randomized trials published in 2004 established docetaxel-based therapy as the standard of care for hormone-refractory metastatic prostate cancer (Tannock 2004; Petrylak 2004).

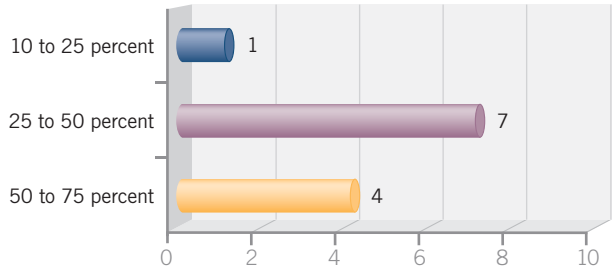
In SWOG-S9916, a combination of docetaxel plus estramustine was compared to mitoxantrone and prednisone (Petrylak 2004). The other study (TAX-327) compared either weekly or every three-week docetaxel with prednisone to mitoxantrone and prednisone (Tannock 2004).

The consistency of the data in terms of survival is remarkable. SWOG-S9916 demonstrated a two-month difference in median overall survival and a 20 percent reduction in the rate of death in favor of the docetaxel-containing regimen (Petrylak 2004).

TAX-327 demonstrated a 24 percent reduction in the risk of death and a two-month difference in median survival in favor of the patients treated with every three-week docetaxel (Tannock 2004).

FACULTY POLL QUESTION 20

Docetaxel-based chemotherapy relieves bone pain from metastatic disease in about which fraction of patients?



SOURCE: Survey of 12 Think Tank Participants, June 15, 2006, Key Biscayne, Florida.

Also important are the quality-of-life improvements seen in TAX-327. Using the FACT-P score, there was an improvement in the quality-of-life parameters in favor of both weekly and every three-week docetaxel compared to mitoxantrone/prednisone, even though weekly docetaxel did not show a survival benefit (Tannock 2004).

In SWOG-S9916, we found that, except for nausea, there were similar quality-of-life improvements with docetaxel/estramustine compared to mitoxantrone/prednisone. This seems to be a comparable regimen in terms of quality of life (Berry 2006).

DR EISENBERGER: In TAX-327, a little less than 50 percent of patients had major pain relief. It is fascinating that when we evaluated the most powerful endpoint to correlate with survival, it was not PSA decline. Rather, it was actually pain relief.

DR SCHELLHAMMER: My impression is that the patients are getting better, with minimal side effects and toxicity, with docetaxel-based chemotherapy. In the big world of chemotherapy, docetaxel seems to be tolerated remarkably well.

DR LOVE: Len, what is your impression of how urologists view chemotherapy for patients with prostate cancer?

DR GOMELLA: I believe this is determined by the attitude of your local medical oncologist. At our institution, they are big believers in second- and third-line hormonal therapy before they commit someone to chemotherapy. If you send a patient with hormone-refractory prostate cancer to a medical oncologist in our local community, they go right to chemotherapy.

DR KEANE: I have five or six patients who have received chemotherapy. It is

remarkable how much better the patients seemed after receiving a course of docetaxel.

A lot of people in the community still live by the old paradigm that chemotherapy is the last resort and can't be used until you have tried everything else. I don't think that holds true anymore, and I think we need to bring medical oncologists into the treatment of prostate cancer earlier and earlier.

DR ZELEFSKY: Dan, is bone pain recognized to be much improved with docetaxel?

DR PETRYLAK: You do see a difference in the bone pain response rates between SWOG-S9916 and TAX-327. It is superior with docetaxel/prednisone when compared to mitoxantrone/prednisone (Tannock 2004), but it is the same in SWOG-S9916 for docetaxel/estramustine compared to mitoxantrone/prednisone (Petrylak 2004). I wonder, if we had prednisone in the regimen, whether there would been a higher rate of pain improvement. ■

SELECT PUBLICATIONS

Arlen PM et al. **A randomized phase II study of concurrent docetaxel plus vaccine versus vaccine alone in metastatic androgen-independent prostate cancer.** *Clin Cancer Res* 2006;12(4):1260-9. **Abstract**

Beer TM et al. **Intermittent chemotherapy in metastatic androgen-independent prostate cancer.** *Br J Cancer* 2003;89(6):968-70. **Abstract**

Beer TM et al. **Weekly high-dose calcitriol and docetaxel in metastatic androgen-independent prostate cancer.** *J Clin Oncol* 2003;21(1):123-8. **Abstract**

Berry DL et al. **Quality of life and pain in advanced stage prostate cancer: Results of a Southwest Oncology Group randomized trial comparing docetaxel and estramustine to mitoxantrone and prednisone.** *J Clin Oncol* 2006;24(18):2828-35. **Abstract**

Berthold DR et al. **Association of pain and quality of life (QOL) response with PSA response and survival of patients (pts) with metastatic hormone refractory prostate cancer (mHRPC) treated with docetaxel or mitoxantrone in the TAX-327 study.** *Proc ASCO* 2006;**Abstract 4516**.

Caffo O et al. **A multicentric phase II randomized trial of docetaxel (D) plus estramustine (E) versus docetaxel (D) as first line chemotherapy for patients (pts) with hormone-refractory advanced prostate cancer (HRPC).** *Proc ASCO* 2006;**Abstract 4625**.

Chan JS et al. **Skeletal related events (SREs) in metastatic androgen independent prostate cancer (AIPC) treated with docetaxel-based chemotherapy: Results from ASCENT.** *Proc ASCO* 2006;**Abstract 4614**.

Ferrero JM et al. **Phase II trial evaluating a docetaxel-capecitabine combination as treatment for hormone-refractory prostate cancer.** *Cancer* 2006;107(4):738-45. **Abstract**

Lucas A, Petrylak DP. **The case for early chemotherapy for the treatment of metastatic disease.** *J Urol* 2006;176(6 Pt 2):S72-5. **Abstract**

Oudard S et al. **Multicenter randomized phase II study of two schedules of docetaxel, estramustine, and prednisone versus mitoxantrone plus prednisone in patients with metastatic hormone-refractory prostate cancer.** *J Clin Oncol* 2005;23(15):3343-51. **Abstract**

Petrylak DP et al. **Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer.** *N Engl J Med* 2004;351(15):1513-20. **Abstract**

Tannock IF et al; TAX 327 Investigators. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following factors is the most predictive for prostate cancer mortality according to Freedland et al?**
   a. Postoperative PSA doubling time
   b. Pathologic Gleason sum
   c. Time from surgery to biochemical recurrence

2. **In the Messing trial comparing immediate versus deferred androgen deprivation therapy in patients with node-positive prostate cancer after radical prostatectomy, which treatment was more efficacious?**
   a. Immediate
   b. Deferred

3. **A presentation at ASCO 2006 demonstrated that the benefits of salvage radiation therapy improved according to the PSA before radiation therapy. The response was best when the PSA was below _____.**
   a. 0.02 ng/mL
   b. 0.2 ng/mL
   c. 0.4 ng/mL
   d. 1 ng/mL

4. **An interim analysis of a Japanese trial evaluating an LHRH agonist with or without bicalutamide as first-line treatment for advanced prostate cancer has shown a benefit for patients who received bicalutamide.**
   a. True
   b. False

5. **EORTC-22911 demonstrated that men with positive margins who received adjuvant radiation therapy after radical prostatectomy had a lower risk of PSA recurrence than men who were observed.**
   a. True
   b. False

6. **In a clinical trial by Stephenson, the response rate to salvage radiation therapy was about _____.**
   a. 25 percent
   b. 40 percent
   c. 65 percent
   d. 100 percent
   e. None of the above

7. **In SWOG-S9921, patients with high-risk disease are randomly assigned after radical prostatectomy to receive immediate hormonal therapy for two years with or without _____.**
   a. Mitoxantrone/prednisone
   b. Docetaxel/estramustine
   c. Weekly docetaxel
   d. Every three-week docetaxel
   e. Any of the above

8. **In SWOG-S9916, patients with hormone-refractory metastatic prostate cancer who were treated with docetaxel/estramustine had a _____ improvement in median overall survival.**
   a. 15-month
   b. 10-month
   c. Five-month
   d. Two-month
   e. None of the above

9. **In a trial of patients with hormone-refractory metastatic prostate cancer, every three-week docetaxel compared to mitoxantrone/prednisone demonstrated a 24 percent reduction in the risk of death and an improvement in quality of life.**
   a. True
   b. False

Post-test answer key: 1a, 2a, 3b, 4a, 5a, 6c, 7a, 8d, 9a

EVALUATION FORM

Prostate Cancer Update — Think Tank Issue 1, 2006

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion will be issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = Not applicable to this issue of *PCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *PCU* Think Tank address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in prostate cancer screening, prevention and treatment and incorporate these data into management strategies in the local and advanced disease settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Inform prostate cancer patients about the specific risks and benefits of local and systemic therapies. . . . . 5 4 3 2 1 N/A
- Provide individualized counseling to patients regarding the choice and timing of endocrine therapy. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients in the high-risk or advanced disease settings about the risks and benefits of chemotherapy, including emerging data on taxane-based regimens. . . . . 5 4 3 2 1 N/A

OVERALL EFFECTIVENESS OF THE FACULTY MEMBERS

To what extent do you feel the faculty members' comments were helpful or not helpful?

. . . . . .

. . . . . .

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity.	5	4	3	2	1	N/A
Related to my practice needs.	5	4	3	2	1	N/A
Will influence how I practice.	5	4	3	2	1	N/A
Will help me improve patient care.	5	4	3	2	1	N/A
Stimulated my intellectual curiosity.	5	4	3	2	1	N/A
Overall quality of material.	5	4	3	2	1	N/A
Overall, the activity met my expectations.	5	4	3	2	1	N/A
Avoided commercial bias or influence.	5	4	3	2	1	N/A

EFFECTIVENESS OF THE SPECIFIC SEGMENTS OF THIS PROGRAM

Which of the following modules did you find particularly relevant to your practice?

- ☐ Multimodality Therapy for High-Risk Disease
- ☐ Treatment for Patients with PSA-Only Relapse
- ☐ Chemotherapy for Metastatic Prostate Cancer

Which of the following audio formats of this program did you use?

☐ Audio CDs ☐ Audio tapes ☐ Downloaded MP3s from website

EVALUATION FORM

Prostate Cancer Update — Think Tank Issue 1, 2006

REQUEST FOR CREDIT — please print clearly

Name: ..... Specialty: .....

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ RN ☐ PA ☐ Other .....

Medical License/ME Number: ..... Last 4 Digits of SSN (required): .....

Street Address: ..... Box/Suite: .....

City, State, Zip: .....

Telephone: ..... Fax: .....

Email: .....

Research To Practice designates this educational activity for a maximum of 3.5 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

Will the information presented cause you to make any changes in your practice?

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

What other topics would you like to see addressed in future educational programs?

.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Additional comments about this activity:

.....

FOLLOW-UP

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

PCUTT106

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at ProstateCancerUpdate.com/ThinkTank.

Prostate Cancer™ UPDATE

Editor/CME Director	Neil Love, MD
Managing Editor	Kathryn Ault Ziel, PhD
Scientific Director	Richard Kaderman, PhD
Writers	Lilliam Sklaver Poltorack, PharmD Douglas Paley
Continuing Education Administrator for Nursing	Sally Bogert, RNC, WHCNP
Content Validation	Margaret Peng Ginelle Suarez Erin Wall
Director, Creative and Copy Editing	Aura Herrmann
Creative Manager	Fernando Rendina
Graphic Designers	Jason Cunnius Tamara Dabney Shantia Daniel Elisa Stambouli
Senior Production Editor	Alexis Oneca
Managing Production Coordinator	Tere Sosa
Copy Editors	Dave Amber Mary DiNunzio Rosemary Hulce Kirsten Miller Pat Morrissey/Havlin Carol Peschke Susan Petrone
Production Manager	Patricia Kappes
Audio Production	Frank Cesarano
Technical Services	Arly Ledezma
Web Master	John Ribeiro
Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Email: CME@ResearchToPractice.net

This program is supported by education grants from AstraZeneca Pharmaceuticals LP and Sanofi-Aventis.

Prostate Cancer™

U P D A T E

This program is supported by education grants from
AstraZeneca Pharmaceuticals LP and Sanofi-Aventis.

Research To Practice®

Sponsored by Research To Practice.

Last review date: December 2006
Release date: December 2006
Expiration date: December 2007
Estimated time to complete: 3.5 hours